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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/541,614	04/27/2006	Yvonne Paterson	P-7772-US	4019

49443 7590 12/09/2009

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
12/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,614	PATERSON ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-21 and 23-30* is/are pending in the application.

4a) Of the above claim(s) *10-19 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2,5-9,20-21,23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 5-21, 22-30 are pending.

Claims 1-2, 5-9, 20-21, 23-27 are under consideration; all other claims stand withdrawn from consideration.

Response to Argument

1. Applicant's arguments filed September 1, 2009 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. The rejection of claims 1, 2, 5-9, 20-21, 23-27 under 35 U.S.C. 102(e) as being anticipated by Pawelek et al (US Pat. 6,685,935, effective filing date June 4, 1996) is traversed on the grounds that:

- The instant method is a method of stabilizing virulence, rather that methods of attenuating bacteria;
- The present application shows that after two passages there is an increase in activity, ie. virulence and enhanced immunogenicity, points to the Instant Application's Figure 1 for support for this statement and the new combination of claim limitations recited in amended claims 1 and 20 and concludes that this activity remains stable throughout subsequent passages, thereby demonstrating stabilization of virulence throughout the passage cycle.
- Pawelek et al does not carry out the instant methods steps until a maximum bacterial load in an organ is reached and discusses genetic manipulation for attenuation of virulence.

3. It is the position of the examiner that Pawelek et al selects for stable virulence factors associated with invasive infectivity of tumor cells, in order to obtain "super-infective" bacteria that attach and infect liver cancer cells, or other types of organ cancers/tumors. The claimed invention does not require any specific virulence factors to be enhanced, and Pawelek et al select bacterial vaccine vectors with enhanced virulence attachment and infectivity factors and therefore meets the requirements of the instantly claimed method.

4. Additionally, Pawelek et al teaches selection of bacterial vaccine vectors for stimulation of an immune response against tumor cells based upon bacterial expression of endotoxins which in turn stimulates/enhance host animal cellular immune responses. Therefore, virulence factors for attachment (adhesion), invasiveness (super-infective) as well as enhanced immunogenicity associated with endotoxin release are virulence factors

that are enhanced by in vivo passage, as well as evidencing reduced host animal toxicity characteristics, based upon selective attenuation of other virulence factors. It was also noted that Applicant describes an attenuated strain of Listeria that is encompassed by the claimed genus of methods; Applicant's traversal is not commensurate in scope with the instantly claimed invention (See detailed description paragraph 274," Salmonella .... stimulated a host cellular immune response to the tumor cells. Enhancement of tumor immunity is thus another potential advantage in the use of parasites as tumor-specific therapeutic vectors." ; "release of the lipopolysaccharide (LPS) endotoxin by Gram negative bacteria such as Salmonella triggers release of tumor necrosis factor, TNF, by cells of the host immune system, such as macrophages, Christ et al., 1995, Science 268:80-83. Elevated TNF levels in turn initiate a cascade of cytokine-mediated reactions which culminate in the death of tumor cells.(Summary text paragraph12),

5. In light of the fact that the claims many select for any type of enhanced virulence factors based upon the claimed methods steps, Pawelek et al who selects for enhanced adhesiveness, super infectivity and endotoxin release virulence factor, these factors resulting in an enhanced immunogenicity of the bacterial cell that gets directed against the infected tumor cell, as well as antigen expression based upon the number of bacteria.

mice. The procedure was repeated through 4 cycles of infection into mice, followed by recovery from tumors. At the beginning of each cycle, the number of bacteria inoculated and the time of infection was reduced from the previous cycle in order to increase the stringency of selection for tumor-specific mutants. The resultant population recovered after 4 cycles was designated #72^{vw-1}. The results of this procedure are detailed in Table 9 below.

TABLE 9

SELECTION FOR MELANOMA SPECIFIC *SALMONELLA TYPHIMURIUM* IN TUMOR-BEARING MICE

Infection Cycle	Total # Bacteria Inoculated/mouse	Infection Time	Total # Bacteria Recovered in Tumors*
1	1×10^{7}	120 min	2.1×10^{7}
2	5×10^{6}	90 min	1.6×10^{8}
3	6×10^{6}	60 min	1.7×10^{8}
4	2×10^{6}	45 min	2.4×10^{8}

* Infecting Salmonella were pooled from 4-5 separate tumors for each cycle

Pawelek et al shows levels of bacteria per tumor that are shown in Applicant's figure 1 and 2 and describes as being maximum load levels. While Pawelek et al does not use the term maximum load, the mouse passaged bacteria were present at a maximum level 10 X $10^{6or\ 7}$ see Table 9 above.

6. Upon consideration of the instant Specification paragraph [0087] and drawings, Figures 1 A (Lm-Gag) & 1B(Lm-LLO-E7) and Figure 2(Lm-E7), the examiner found the Specification to teach "the number of passages in an animal is not limited to a fixed number" but rather is determined by the bacterial load harvested from the animal [0087] and Figures 1 A& B are data obtained by using specific mutant recombinant strains of Listeria which are not claimed [0145]. Figure 2, shows data from an additional strain of Listeria that expresses some virulence factors, a strain that did not reach maximum load after the "second passage", the phrase "second passage" means "passage 1" as shown in Figure 2 (see [0087 of instant Application PG-Pub for definition of "second passage" and "passage 1"]) as the number of bacteria per load still increased in the third passage (passage 2).

- ❖ Therefore all Listerial strains disclosed in the instant Specification do not reach maximum load by the second passage as asserted, nor does the instant Specification teach that all bacterial vectors reach maximum load by the second passage based upon the guidance and teaching provided in [0087] of the instant Specification that states "the number of passages in an animal is not limited to a fixed number".

7. With respect to virulence stability being achieved "following the second passage of the bacterial vaccine vector ", the examiner could not find support for the newly claimed genus of bacterial vaccine vectors with the claimed functional characteristics. Pawelek et al discloses repeating the claimed methods steps, and therefore produced strains of bacterial vaccine vectors that would inherently evidence the claimed functional characteristics based upon the carrying out the same or equivalent methods steps based upon successive administration, passage and harvesting of the bacterial vaccine vectors to

achieve "super infective" bacterial strains:(see section 6.1.2 "Cycling the microorganism through solid tumors in vivo", see col. 16, line 51-63) that are able to express a heterologous antigen. Also see Definitions for "Super-infective" which are detectably infectious to target tumor cells at a ratio of 90:1 relative to wild-type cells (Pawelek et al, brief summary text paragraph 55). The super-infective bacterial strains are stable, as they are "able to distinguish between a cancerous target cell and non-cancerous counterpart cell so that the vector preferentially attaches to, infects and/or remains viable in the cancerous target cell." While Pawelek et al does not utilize the same terms to describe their invention, the method steps and bacterial vectors are the same or equivalent methods steps and bacterial vaccine vectors that stably express virulence factors and the heterologous antigen in such a way that they are able to maintain viability intracellularly and induce the desired immune response to enhance tumor killing.

Pawelek et al still anticipates the instantly claimed invention as now claimed for reasons of record and responses set forth herein.

New claim Limitations/New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 5-9, 20-21, 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. Applicant has amended all of the claims to recite a new combination of functional claim limitations : " and whereby the maximum bacterial load is reached and virulence is stabilized following the second passage of said bacterial vaccine vector".

11. Upon consideration of the instant Specification and the guidance and teaching provided therein, the examiner did not find a genus of bacterial vaccine vectors that stably express induced virulence factors following the second passage.

a. Figure 1A and 1B show strains of Listeria that at passage 1 (which is the second passage) were not be at maximum load by the second passage based upon the formula provided in Applicant's Specification at paragraph [0087],

b. Figure 2 shows a strain that also did not reach maximum load by passage 1(second passage) but increased numbers of bacteria were found in passage 2 (third passage).

c. Additionally, the Specification teaches [0087, whole paragraph] that maximum load is realized when a subsequent passage produces a reduced number of bacteria as compared to the prior passage, at which point the prior passage is determined to have reached maximum bacterial load. Figure 2 does not show any reduction in bacterial load with subsequent passage after the second passage, so maximum load can not be assumed to have been reached at the second passage. Figures 1 A & B also do not show a reduction in bacterial load in passages 2, 3 and 4 or passages 2, 3, respectively, but show a leveling off of bacterial load. A leveling off of bacterial load is not discussed in the description of how to

determine maximum load described at paragraph [0087] of the instant Specification.

The instant Specification teaches at [0087] a method of determining maximum load, the process repeating the claimed methods steps as many times as required to reach maximum load, there being *no guarantee that the bacterial strains will all function identically*, but each passage must be evaluated through counting the number of bacteria found in the current passage as compared with the prior passage and when the current bacterial load is less than the prior passage, then maximum load would have been achieved in the prior passage.

Therefore, the newly submitted combination of functional limitations do not have original descriptive support in the instant Specification based upon the disclosure and figures to which Applicant pointed as support for the newly claimed genus of methods that utilized a genus of bacterial vaccine vectors that express virulence factors stably after the second passage (passage 1, def of term see [0087]), Therefore all of the claims recite New Matter.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-2, 5-9, 20-21, 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are:

d. Claims 1 and 20 have been amended to require the passaged bacteria to have stabilized virulence factors following the second passage of the bacterial

vaccine vector. What the virulence factors are that will remain stable after the second passage is not specifically claimed. In what environment are the virulence factors required to be stable?

e. The virulence factors appear to be inducible virulence factors based upon passage of the bacterial resulting in enhanced expression of the factors with passage, but since the virulence factors are inducible, they also can be repressed if the environmental factors that induced them through passage are removed upon harvesting the bacterial vaccine vector from the organ.

f. Virulence stability is now required to be stable following the second passage of the bacterial vaccine vector, how long does this stability last? How is expression of the heterologous antigen linked to bacterial load? When in the growth cycle is the heterologous antigen expressed? Where in the bacterial vector is the heterologous antigen expressed (exported or in an inclusion body)? How is the heterologous antigen linked to stable expression of virulence factors through passage?

g. The virulence factor recited in the claims can be any type of virulence factor that can be enhanced based upon passage through an animal host, the essential element linking the heterologous antigen expression with induced virulence factor expression is missing from the claimed. Some virulence factors are environmentally induced based upon temperature, nutrients, host animal, growth environment being intracellular or extracelluar to name a few. It is not clear to the examiner how the virulence factors that are inducible are stable following the second passage indefinitely, especially when the instant Specification teaches at [0087] that the number of bacteria can actually decrease with number of passages . The reduction in bacterial load after

repeated passage, after having reaching maximum load, could possibly due to loss of expression of some virulence factors "following the second passage". What are the virulence factors that are stabilized?

In summary: The essential element that stabilizes virulence factor expression following the second passage of the bacterial vaccine vector is missing from the claims as well as the essential element that links expression of the heterologous antigen with animal passage and stabilization of inducible virulence factors. The claimed invention is missing essential structural elements for the recited functional characteristic.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1,2,7-9, 20-21, 25-27 rejected under 35 U.S.C. 102(b) as being anticipated by Coulson et al (Vaccine, 1994).

Coulson et al disclose the instantly claimed invention directed to a method of enhancing the immunogenicity of a bacterial vaccine vector, the method comprising the steps of:

Step a) Administering (either iv or orally, see page 1398, col. 1, p. 1 and 2) to an animal (mice) the bacterial vaccine vector (see page 1398, col. 2, p. 1 " S. typhimurium administered iv into groups of mice" or orally (see col. 2, p. 2, last sentence)),

b) Passaging the bacterial vaccine vector through the animal (see page 1398, col. 2, "mouse-passaged strain"),

c) Harvesting the bacterial vaccine vector from the animal ("livers and spleens were removed and bacterial enumerated", page 1398, col. 2, p. 1).

Repeating steps a, b and c (selected clone G3, of S. typhimurium SL3261/pORF1 after the first passage, and used clone G3 to "prepare bacterial suspension for testing in ampicillin-dosed mice"(page 1398, col. 2, p. 2, middle of paragraph),

Wherein maximum load is reached (see Figure 3, SL3261, Liver and Spleen, Table 1, Table 2 and page 1399, col. 2, p. 3 " in vivo cultured bacteria. The ability of the animal-passaged bacterium (clone G3) to colonize host tissues was markedly increased, to levels similar to that found with the wild-type bacteria" and "G3 host can carry these plasmids stably and colonize at high levels", page 1398, p. 2 "Clone G3, which was shown to produce rPA", a heterologous antigen from Bacillus anthracis) and

Virulence stabilized (The mouse passaged strain resulted in **enhanced colonization ability** (increased virulence factor, see abstract) in liver and spleen cells of the mice (see abstract, page 1395 and page 1399, col. 2, p. 3 "markedly increased") and

also evidenced increased stability of plasmid in vivo, the plasmid encoding a heterologous antigen that was expressed, and the expressed heterologous antigen inducing partial protective immunity against challenge with Bacillus anthracis (see Table 2, 33% survival relative to negative control which was 7%).

The oral route of administering S. typhimurium G3 was partially effective in inducing a protective response against B. anthracis (see page 1399, col. 2, last paragraph bridging to page 1400, col. 1) and induced an enhanced cell mediated immune response (CMI) to provide partial protection against challenge (see Table 2, and col. 1, page 1400, p. 3) relative to control strains of bacteria that were not animal passaged (cultured cells lost the plasmid, and therefore considered to be unstably transformed, see page 1398, col. 1, p. 1, first couple of sentences).

Coulson et al disclose the newly claimed functional limitations to be associated with their disclosed method of passaging a bacterial vaccine vector, the method of animal passaging resulting in *increased maximum bacterial load* (marked increased ability to colonize host tissues, p. 1399, col. 2, p. 3) together with *stabilized virulence factor expression* (colonization factors enhanced/increased, see abstract, and page 1398, col. 2, p. 3 "Clone G3, which was shown to produce rPA"). Coulson et al anticipates the instantly claimed invention as now claimed.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
December 3, 2009
/Robert B Mondesi/
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